OCULAR MANIFESTATIONS OF LEPROSY AND ITS MANAGEMENT

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CERTIFICATE

This is to certify that this dissertation entitled **"*OCULAR MANIFESTATIONS OF LEPROSY AND ITS MANAGEMENT*"** has been done by ***DR. S.S. SUBHA*** under my guidance in Department of OPHTHALMOLOGY, Madurai Medical College, Madurai.

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DECLARATION

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This is submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfillment of the requirement for the award of M.S.,(Ophthalmology) Branch-III degree Examination to be held in MARCH 2009.

Place : Madurai

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CONTENTS

INTRODUCTION

Hansens disease is a granulomatous infectious disease caused by Mycobacterium leprae. It affects mainly peripheral nerves but it can also affect skin, muscles, eye, bone, testes and internal organs.

Although much improved in last 25 years, knowledge of the pathogenesis, course, treatment and prevention of the disease continues to evolve. The skin lesions and deformities were historically responsible for stigma attached to the disease. The introduction of MDT in early 1980 had begun to have an impact on the transmission of disease and severity of its attending complications.

Eye involvement in leprosy is quite common. Its complications, particularly sight threatening complications, if neglected will lead to blindness.

Good vision is required not only for performance of routine activities but also for the care of anaesthetic hands and feet. Loss of eyesight in a person who already have anaesthesia in hands and feet is a disaster.

Ocular lesions range from chronic irritation of eyes to blindness. The incidence of eye involvement in leprosy is stated to be anywhere from 15 % (tuberculoid) to 100% in long standing lepromatous leprosy.

Ocular involvement had been seen even in patient who have completed the MDT. Every year, approximately 5.6% of patients with multibacillary leprosy who completed MDT can be expected to develop new ocular complications of leprosy which often (3.9%) are potentially vision threatening. Similarly complications can occur during MDT therapy and during relapse of the disease.

Ocular morbidity like orbicularis weakness and lagophthalmos are found to be more in patients with reversal reaction. Elderly, deformed, skin smear positive lepromatous patients are associated with increased ocular morbidity and form a group that require acceptable and accessible eye care.

This study aims at determining the incidence of various ocular manifestations of leprosy and its management.

MYCOBACTERIOLOGY

MORPHOLOGY :

Mycobacterium leprae belongs to Actinomycetales and family Mycobacteriaceae which are rod shaped aerobic and non sporing bacteria. The organism does not stain readily but once stained they resist decolourisation by acid or alcohol and hence called acid-fast bacillus. It occurs singly in parallel bundles or in globular masses and often found within endothelial cells of blood vessels, in mononuclear cells or in schwann cells and is the only mycobacterium that infects peripheral nerves. Its long generation time (12-13 days) is responsible for chronicity. The bacteria involves cooler tissues of the body such as skin, superficial nerves, nose, pharynx, eyes and testicles. This organism was described by Armauer Hansen in 1873 .

CULTIVATION :

It has not been cultivated on non-living bacteriological media. (Dasypus novemcintus) the nine branded armadillo is susceptible to mycobacterium leprae possibly because it has a low body temperature. About 40% of Armadillos inoculated with Mycobacterium leprae develop florid lepromatous leprosy, both clinically and histopathologically after a year or more.

However real break through was discovered by Shepard (1960) that leprae bacilli could multiply in footpad of mice kept at low temperature20 degree Celsius. Following intradermal inoculation into footpad of mice, a granuloma develops at the site in 1-6 months.

This technique had been utilized in diagnosis of the disease, evaluation of potency of antileprosy drugs and detection of viability of the bacilli during treatment.

One of the best known reports of cultivation is from Indian cancer research center Bombay where AFB was isolated from leprosy patients employing fetal ganglion cell culture.

Resistance :

Lepra bacilli is found to remain viable in a warm humid environment for 9-16 days and in moist soil for 46 days. They survive exposure to direct sunlight for 2 hours and UV rays for 30 minutes.

HISTORICAL BACKGROUND

The history of mans relationship with leprosy has always invoked a great deal of speculation.

Word leper is derived from Greek language. The word leper means scaly. The disease is thought to have had its origin in Asia. The earliest records of leprosy like disease is from India and China as early as 600 B.C. In India leprosy has been known since ancient times as kustha roga (in Sanskrit). Chaulmoogra oil was used as treatment for kustha roga.

The earliest evidence of leprosy is the mummies of second century B.C. The disease probably was carried from India to Europe in fourth century B.C by the returning Greek soldiers. From Greece, the disease spread slowly throughout Europe where the maximum period of activity was between tenth and fifteenth centuries. Subsequently the disease underwent a steady and significant decline to 1/1,00,000 by the year 1900, due to the strict isolation of patients and improvement in the quality of life of the people .

For a long time the disease was thought to be a curse or punishment from God. It was only after several centuries that the causative organism-Mycobacterium leprae was discovered by Armauer Hansen of Norway in 1873, yet there was no effective remedy for the disease . For long time the only way to handle leprosy patients was to isolate them for life in special

situation. With the introduction of sulfone drugs in the treatment of leprosy in 1943 marked the beginning of new era- the era of case finding and domiciliary treatment

With this and the magnitude of the disease in our country in mind, the government of India launched the National Leprosy Control Programme (NLCP) in 1955.

The development of experimental animal models occurred in 6o and 70”s. In 1960 – Shepard discovered M.leprae could multiply to certain extent when injected into footpads of mice .In 1971 Krichheimer in USA paved the way for vast experimental work in leprosy research. He reported that armadillos developed disseminated leprosy when injected experimentally with M.leprae.

Thus NLCP in India was redesigned as NLEP (National Leprosy Eradication Programme) in 1983, with the goal of arresting the disease, by the start of twenty first century.

EPIDEMIOLOGY

The evolution of leprosy as a disease has been slow that its epidemiological pattern, probably extending over several centuries was poorly documented than acute disease such as plaque worldwide.

The disease and its various clinical forms is not uniformly distributed. The disease had died out completely in Northern Europe, Hawai, Japan, Venezuela, United States of America. This is due to economic development in these countries leading to change in risk factors. It is still endemic at a low level in part southern and Eastern Europe, South east Asia, Africa and Western pacific where poverty and low standard of living still persist. Estimated number of cases is about 10-12 million. Accurate assessment is not possible because the endemic population are those of developing countries where reporting systems are poor.

Leprosy :

Leprosy is a major health problem in India. According to WHO expert committee, a public health problem is said to exist when the prevalence of leprosy is around 1/4000 population.

In 1981 number of cases is about 4 million. Prevalence being 5.7 /1000 population. Almost all states in India have a leprosy problem, there is a great degree of variability. The disease is more prevalent in southern and eastern regions than in northern region of the country. States maximally

affected are Tamilnadu, Pondicherry, Bihar and Orissa with prevalence being >5/1000 population.

Ocular complications occur in 10%-90% of patients and probably occur more frequently during leprosy than in any other systemic infectious disease. Approximately 5% - 10% of patients with ocular leprosy are blinded by the disease and a million or more leprosy patients have substantial vision loss from leprosy.

CLASSIFICATION

Leprosy has been classified based on clinical, bacteriological, immunological and historical status of patients. The following are various classification:

Indian classification :

- Indeterminate type
- Tuberculoid type
- Borderline type
- Lepromatous type
- Pure neuritic type

Matrid classification :

- Indeterminate
- Tuberculoid- flat : raised
- Borderline
- Lepromatous

Ridley and jopling classification :

According to their position on immunological scale it is divided into

- Tuberculoid (TT)
- Borderline tuberculoid (BT)
- Borderline (BB)
- Borderline lepromatous(BL)
- Lepromatous type (LL)

The Indian and matrid classification systems are the most widely used classifications in leprosy field programmes, whereas Ridely

and Jopling classification can be used only when full research facilities are available.

CLINICAL FEATURES OF LEPROSY

Cardinal signs of leprosy :

Mycobacterium leprae (causitive organism)

↓

Affinity to nerves

↓

Inflammation

↓

Enlargement and tenderness of nerves

↓

Further inflammation → loss of nerve tissues → loss of function

↓

Sensory fibers are affected first leading to loss of sensation in the skin lesion (or) in the area supplied by the nerve.

Atleast any one of the above three signs must be there to diagnose leprosy.

Leprosy by WHO case definition :

A person having one / more of the following features

1) Hypopigmented / reddish skin lesions with definite loss of sensation
2) Involvement of peripheral nerves as demonstrated by definite

thickening with loss of sensation.

3) Skin smear positive for AFB

Systemic features :

Mycobacterium leprae regardless of the route of entry into human body, only a proportion of persons infected develop signs of the disease after the incubation period of 3-5 years. Majority will develop sub-clinical infection. The initial sites of infection are the peripheral nerves with target organ being schwann cell. Thus the most common first symptom is a small but persistent area of impaired sensation/numbness. In others, first noticeable feature may be macules which are usually hypopigmented and erythematous .

Tuberculoid leprosy :

Skin lesion :

It is documented by few (usually 3) solitary lesions affecting skin and peripheral nerves. The margins are usually well defined, with dry and rough surface. The lesions are firm in consistency. There is no central healing. It is usually associated with loss of hair, loss of sweating and anaesthesia. Lesions are usually asymmetrical.

Nerve lesions : Nerve involvement is common in this type of leprosy. Nerves close to the skin lesion are usually affected. Nerve abscess are more common. Systemic involvement is less common.

Lepromatous leprosy :

Skin lesions :

Lesions are ill defined, multiple, with smooth surface and soft in consistency. Lesions are usually symmetrical.

Nerve involvement :

Nerve involvement occurs in late stage. Multiple nerves are affected.

Systemic involvement :

Systemic involvement is more common and severe in lepromatous leprosy. Eye , nose , larynx and testes are involved .

Ocular features of leprosy :

Blindness is common and disastrous complication in leprosy. In 1873 Hansen stated “There is no disease which so frequently gives rise to disorders of the eye as leprosy does”. The ocular adenexa and anterior segment of the eye offer an ideal site for the proliferation of M.leprae. The cooler temperatures, the presence of a rich neurovascular network and the possibility of ocular immunologic compartmentalization may all be incriminated as contributing to ocular complication during leprosy. Ocular complications occur in 1/3 of leprosy patients.

For simplicity ocular lesions are classified into two groups. The first group include potentially sight threatening lesions (PST) which includes

lagophthalmos and its sequelae, chronic iridocyclitis and its sequelae. Lesions such as loss of eyebrows and eyelashes have no visual significance but contribute to the stigma which these patients endure.

Process by which eye can be damaged :

1) Exposure and anaesthesia :

Involvement of occipital, temporal and zygomatic branches of the facial nerve produce selective paralysis of orbicularis oculi muscle. This is usually seen to occur during type I reactions and in untreated lepromatous leprosy on later stages.

Bacillary infiltration of the superficial muscles of the face also cause weakness in lepromatous leprosy. Lagophthalmos develops and blinking is incomplete. Cornea and conjunctiva become prone to drying and to minor trauma. In tuberculoid lesions of face, entropion and trichiasis develops due to scarring of the tarsal plate.

2) Bacillary invasion :

Bacillary invasion of the eye occurs through both the blood stream and via the corneal nerves, thus mainly involving cornea and ciliary body.

3) Hypersensitivity :

Iris and ciliary body that have been involved by the leprosy bacilli are prone to severe damage during type 2 lepra reaction. These

may be the sites of deposition of circulating immune complexes even when there is no bacilli.

Ocular manifestations of leprosy :

Eyebrows	-	Madarosis
Lids	-	Lagophthalmos
	-	Entropion
	-	Ectropion
	-	Trichiasis
	-	Lid nodules
Meibomian glands	-	Tear film abnormalities
Lacrimal glands	-	Acute and Chronic Dacryoadenitis
Sclera	-	Scleritis
	-	Episclerits
Cornea	-	Hypesthesia
	-	Avascular keratitis
	-	Corneal leproma
	-	Interstitial keratitis
Iris and ciliary body	-	Acute and Chronic
	-	Iridocyclitis
	-	Iris leproma

Lens	-	Complicated cataract
Raised IOP	-	Secondary open angle Glaucoma
Posterior segment	-	Choroidal and retinal pearls
	-	Choroiditis

External adenexal involvement :

Eyebrows :

Thinning of eyebrows and subsequent loss is one of the most common manifestations of leprosy. This begins temporally and progresses nasally probably because temporal brow is relatively cooler. Brow loss may be total and permanent.

Eyelids :

Seventh nerve palsy results in lagophthalmos, lower lid ectropion, occasionally upper lid entropion and poor lacrimal drainage. All leprosy patients regardless of their clinical disease are at at risk of developing lagophthalmos. Paucibacillary patients and those in reversal reaction develop paralytic lagophthalmos earlier and suddenly. Multibacilary patients develop paresis later in the disease and often also develop anaesthesia of cornea and conjunctiva due to involvement of trigeminal nerve.

Fifth and seventh nerve involvement leads to exposure keratitis(neuroparalytic and neurotrophic), dry eyes, dermalization of

cornea and conjunctiva. Trichiasis, susceptibility to trauma resulting in corneal scarring and **blindness.**

Eyelid nodules and placoid lesions develop in paucibacillary, reversal, ENL reaction. There is a positive correlation between type 1 reaction lesions on the face and subsequently lagophthalmos which may identify those patients who are at risk of developing corneal blindness from exposure keratitis. Loss of skin elasticity, infiltration of marginal and pretarsal fibers of orbicularis oculi muscle by M.leprae and loss of muscle tone contributes to dermatochalasis and heavy drooping upper lids. Further atrophy at the canthal tendons and tarsal plates creates heavy floppy lids allowing ectropion perhaps entropion and trichiasis.

Meibomian gland :

Meibomian gland infiltration leads to atrophy and inadequate lipid production with associated tear dysfunction.

Lacrimal gland and lacrimal sac :

Acute and chronic dacryoadenitis arising from cellular infiltration and inflammation of lacrimal gland may occur in lepromatous leprosy. In tuberculoid lesion, denervation of gland results in keratoconjuntivitis sicca Severe nasal infiltration and mucosal scarring lead to NLD obstruction and subsequent dacryocystitis in lepromatous patients.

Cornea :

M.leprae invades cornea through rich network the rich network of limbal ciliary nerves during early stage. Hematogenous spread occur later by way of blood vessels of corneal pannus.

Corneal hypesthesia may be found in all forms of the disease and may lead to inadequate blink reflex which coupled with lagophthalmos, ectropion and dry eyes leads to typical inferior **exposure keratoconjunctivitis** . This is an early warning sign of inadequate protection and increased risk of bacterial corneal infection and may leading to blindness.

Enlarged edematous cornea nerves are found in lepromatous leprosy. The nerve involvement has the appearance of focal swelling resembling "**bead of string** "and consists of M.leprae and a surrounding granulomatous response within the cranial nerve.

These nerve swellings are pathognomonic of leprosy and may be the first sign of ocular and systemic leprosy. The nerve changes represent granulomatous reactions that resolve spontaneously. Following treatment lesions sometimes calcify and persist. Later it leads opacification of cornea.

Avascular keratitis is characterized by the development of chalky white punctate subepithelial opacities that are first seen in superior

temporal quadrant near the limbus. They are usually found in asymptomatic non-inflammed eye.

Historically the lesion represents miliary lepromas and consists of macrophages packed with leprae. The lesion becomes gradually confluent and less demarcated causing surrounding cornea hazy. Later there is a destruction of bowmans layer and superficial vascularisation produces the classical lepromatous pannus.

Corneal lepromas appear as large white or yellowish nodules at the limbus. They represent large granulomata and are relatively infrequent except in Japan and South America. They occasionally encroach upon the visual axis.

Interstitial keratitis begins in superotemporal quadrant and represent a more severe form of avascular keratitis that progresses to necrosis and later avascular invasion.

Sclera :

Nodular episclerits and **scleritis** usually consists of focal leproma and an inflammatory response. Diffuse episcleritis and scleritis may also occur as an immunologically driven disease with immune complex deposition without direct bacillary invasion. It is typically observed during lepra reactions and is often associated with keratitis or iridocyclitis.

Chronic / recurrent scleritis may lead to scleral necrosis, scleral melting and staphyloma.

Iris and ciliary body :

Uveal tract involvement is primarily seen in lepromatous leprosy and its incidence is directly proportional to disease duration.

Lepromatous iridocyclitis :

It may be 1) Caused by direct invasion of M.leprae into ocular structures, hematogenous or by the way of ciliary nerves.

2) Neuroparalytic - as a result of early involvement of iris sympathetic nerves.

Evidences for neuroparalytic iritis are :

1) **Organismal** :

   a) Preferential attachment of lepra bacilli to nerves in various organs, a similar manner of affliction may occur in iris.

   b) Preferential lodgement of organisms in cooler parts of the body (testes, nose ,ear). As iris temperature is 3.6 degree less than the body temperature (Schwartz – 1962) it can be preferential site.

2) Clinical :

a) Sluggishly reacting pupils with anisocoria without overt signs of uveitis goes in favour of neuroparalytic basis.

b) Corneal nerve involvement is a well known clinical entity in leprosy. A parallel situation might occur in iris.

3) Pharmacological :

a) Early autonomic denervation hypersensitivity has been described by Bauschard and Swift (1972) in which pupils of lepromatous patients responded positively to epinephrine in an abnormal way.

b) Poor response to anticholinergic drugs like atropine as the basic fault lies in adrenergic nerve fibres.

4) Histopathological :

Lack of organisms in aqueous / iris and functional changes are much more marked as compared to organic iris changes.

A uveal hypersensitivity to M.leprae has been isolated from normal appearing eyes and it has been that iris is a site in which M.leprae might survive long after skin smears have become negative. Early subtle involvement includes diminished pupillary reactions, denervation hypersensitivity to adrenergic agents and reduced accommodation.

Iris involvement can be divided into

1) Acute diffuse plastic iridocyclitis :

Acute non-granulomatous iridocyclitis is a common often bilateral accompaniment of type 2 reaction. Its clinical presentation is similar to other non- leprous iritis. The course of the disease is often fulminant with a sudden painful onset, conjuctival hyperemia, keratic

precipitates, aqueous cells often with hypopyon formation , posterior synechiae and secondary glaucoma. Spontaneous hyphaema may also occur as a result of fragility of iris vasculature.

2) Chronic iridocyclitis :

The more common chronic iridocyclitis is less dramatic but potentially blinding. It is a low grade granulomatous or non-granulomatous iridocyclitis common in lepromatous leprosy but also seen in tuberculoid form. It is characterized by a lack of symptoms and overt signs. Although slit lamp examination may show aqueous cells and flare with keratic precipitates scattered all over corneal endothelium. Its chronic course leading to iris atrophy and polycoria. Iris adhesions progress to seclude and occlude the pupil. Small non-reacting pupils caused by the involvement of sympathetic iris nerves, exaggerate visual impairment created by developing lens changes and corneal opacities.

The presumed pathogenesis of chronic lepromatous iritis is that during primary bacteremia, bacilli lodge in autonomic fibres of iris and cause a slow degeneration of nerves which cause a muscular atrophy . Due to atrophy of muscular toxins are released which causes a low grade uveitis with mild flare, KP’s and cells with eyes remaining essentially white and asymptomatic.

3)Miliary iris lepromas :

There are small glistening white lesions which are pathgnomonic for leprosy. They represent aggregates of tightly packed living and dead bacilli lying within mononuclear cells. Iris pearls usually develop within a year or two of the commencement of iritis with little accompanying inflammation or foreign body reaction.

Iris pearls are situated mainly at the papillary margin around the collarette resembling a necklace. Pearls may also develop in slowly increase in size and may tend to aggregate. They become pedunculated and may eventually drop in AC where they are well tolerated and produce no reaction.

4) Nodular iris lepromas :

Bacterial invasion of the iris may also give rise to the formation of nodular leproma which are yellow globular polymorphic masses that occur less commonly than the iris pearls. They occur rarely disrupt the architecture.

5) Iris atrophy :

In lepromatous leprosy the so called chronic iritis produces iris atrophy with small non-reacting pupils which exaggerate the visual impairment created by developing lens changes and corneal opacities. The cause of this chronic iritis is believed to be neuroparalytic from

early involvement of the small nerves of the iris particularly autonomic supply.

Histopathology discloses far more silent chronic iridocyclitis in leprosy patients that are diagnosed clinically. AFB can persist in this tissue even after completion of MDT. Smooth muscle disruption and destruction a cause of miotic pupil in leprosy has been conclusively demonstrated histopathologically. Iris atrophy continues to develop in 3% patients with multibacillary leprosy. Every year after they complete 2 year course of MDT and is associated with age, increasing loads of mycobacteria, sub-clinical cataract and corneal opacity.

6. Posterior segment lesions :

Uveitis in leprosy spares choroids because organisms predilection for cooler parts of the body. Rarely choroidal pearls and retinal pearls in posterior pole affecting vision has been described. Chorioretinal involvement can be in the form of proliferation of RPE, hypopigmented patches, peripheral non- specific choroiditis, disseminated choroiditis, as well as colloid degeneration in the macula. These are non-specific and are the result of reaction to the sensitized uveal tract.

Ocular complications :

Ocular hypotony :

Decreased IOP are typically found in patients with iridocyclitis . Chronic uveitis affects secretory ciliary epithelium of ciliary body and prevents its function and hence hypotony. Abnormalities in the autonomic innervation also contributes to ocular hypotony.

Glaucoma :

Glaucoma is often unrecognized and untreated complication of leprosy. Secondary open glaucoma with history of chronic uveitis and chronic angle glaucoma after intra ocular inflammation are most prominent types . POAG and acute angle closure glaucoma caused by iris bombe also occur.

Cataract :

Primary and secondary cataract formation is responsible for nearly half of blindness in leprosy. A possible cause of cataract formation in leprosy is the reaction of M.leprae with dopa produces high local concentration of quinones which are cataractogenic.

Direct invasion of lens by M.leprae have never been demonstrated. Cataract can occur secondary to anterior segment damage particularly iridocyclitis. Cataract is the most common cause of blindness in leprosy and the social stigmata of the disease often exclude patients from receiving surgery.

GENETICS

The following genes have been associated with leprosy. Hence, susceptibility to leprosy may be atleast partially inheritable.

- Susceptible loci on chromosome band 10p 13 and choromosome 6.
- Polymorphisms in the gene promotor regions of TNF (mutibacillary leprosy) and interleukin (IL-10)
- HLA – HLA-DR2 and HLA –DR3 (tuberculoid disease) as well as HLA- DQ1 (lepromatous leprosy)
- TLR2 mutation in lepromatous leprosy
- Polymorphisms in NRAMP1 gene in multibacillary disease in African patients.
- Genetic variants in the shared promotor region of PARK2 and PACRG genes.
- Taq1 polymorphism (tt genotype) at exon 9 of the vitamin D receptor gene.

IMMUNOPATHOLOGY OF LEPROSY

Host response :

The varied and protracted manifestations of leprosy arise from immunological response of the host against the virtually non-toxic M. leprae. Glycolipids are the important surface antigens of mycobacteria . Phenolic glycolipid I is unique to mycobacterium leprae. It has immuno dominant trisaccharide segment and serves as a valuable chemical marker for M.leprae infected tissues. Recent studies suggest HLA DR2 association with tuberculoid leprosy.

Humoral immunity :

Humoral response in leprosy is not impaired, as patients usually have raised levels of serum immunoglobulin. Peripheral blood- B cells, the producer of antibodies against M.leprae have been demonstrated in lepromatous leprosy. They have been found in the Ig G and Ig M classes. The cell wall of M.Leprae protects it against these specific circulating antibodies. Antibodies are harmful when they react with M.Leprae antigen in the tissues, during type II reactions with the deposition of immunoglobulin and complement in damaged tissues. Complement is raised in patients having lepra reaction. Seropositivity proceeds in all types of leprosy, particularly in LL patients who have very high antibody levels at the time of diagnosis. This is used in the identification of individuals progressing towards lepromatous form.

Cell mediated immunity :

Cellular immunity is normally responsible for limited bacterial multiplication and is therefore essential for protective immunity and resistance against leprosy. In tuberculoid leprosy cell mediated immunity is strong and humoral response is weak, whereas the reverse is true in lepromatous leprosy.

In lepromatous leprosy there is profound and specific deficiency of cell mediated immunity to M.leprae which persists even after prolonged chemotherapy. It suggests that it may be responsible for high risk of relapse in these patients. M.Leprae is present in T- lymphocytes of LL patients. There is insufficient production of IL-2 which results in failure of proliferative T-cell lymphocyte response and macrophage activation upon exposure to M.leprae.

Several theories are there for the development of leprosy. One theory propose that leprosy patients has hereditary cellular immunodeficiency that cause them to be unable to count an effective resistance. The other theory suggests that in early stage, a few replicatory organisms gain access to peripheral nerves where they are hidden from immune surveillance system. Later as they multiply immune tolerance develops producing a cellular immunodeficiency state.

Aetiological factors to immunological response in leprosy :

Though, it is accepted that the outcome of M.leprae infection depends upon the host immune response. The reason for this diminished cell mediated immunity is not exactly known. Various possibilities suggested are :

Genetic constitution:

I. A possible association between leprosy and HLA haplotype has been suggested by several workers but evidences are not conclusive.

II. Primary fault on T-cells there by rendering them unable to stimulate macrophages.

III. Primary fault in macrophages thus making them unresponsive to T cell stimulation.

IV. Suppressor cell activity – According to this hypothesis , there exists a sub population of T-cells (suppressor cells) which decrease the immune response, but several contradictory observations have been made by others.

V. Abnormal antigen presentation :

For a normal and effective cell mediated immunity to occur against Mycobacterium leprae-leakage of bacillary antigens should occur to the regional lymph nodes rather than to central lymphoid component (spleen , thymus, bone marrow) which results in a

humoral response and a suppressed cellular response . In leprosy there is a continuous leakage of bacilli into circulation from the affected nerves as they do not have true lymphatics , thus eliciting a stronger humoral than a cellular response.

Immunopathology of uveitis :

Uveal involvement is more common in patients with disease of longer duration and in patients on irregular treatment especially those belonging to the lepromatous type. Anti-prostaglandin -1 and anti-LAM-B antibodies were significantly higher in patients with ongoing uveitis but who were skin smear negative. Thus insufficient chemotherapy and thereby incomplete elimination of bacilli are the risk factors for occurrence of uveitis in the quiescent stage of the disease. The role of immunogenetic factors in the pathogenesis of uveitis in leprosy has also been extensively studied and it has been suggested that there is an association between HLA-DR2 antigen and susceptibility to uveitis in these patients.

Reactions in leprosy

The chronic benign course of leprosy at times , interrupted by acute episode reactions which may cause irreversible damage if left untreated.

History :

Though Danielsson et all and Hansen et all described a peculiar eruption in lepromatous leprosy resembling Erythema nodosum, clinically it was Muruta in 1912 who first named the condition Erythema nodosum leprosum based on clinical and histopathological features. But ENL was not clearly separated from other reactional states of leprosy until 1950' s when Cochrane put forward classification. Real breakthrough was made by Ridely based on his observation on the histology of these lesions.

Classification (Jollife)

1. Type 1- Leprae reaction comprising of upgrading and downgrading reactions.
2. Type 2 – Erythema nodosum leprosum.

Incidence :

Though it is difficult to determine the incidence of lepra reaction, most authors agree that it's occurrence has decreased since the advent of the sulfones. A high incidence of about 40%-50% of all forms of lepra reactions have been reported.

Clinical features :

Reactional states occur in about one third of patients and are due to acute inflammation of the disease. A lepra reaction should be considered as a medical emergency requiring immediate care. These states can result in

permanent neurological sequelae resulting in disability and deformity. Patients at highest risk are those with multibacillary leprosy and / or pre-existing nerve impairment.

I. Lepra reactions type I (reversal) reactions usually affect patients with borderline disease. Reversal reactions shift toward the tuberculoid pole after start of therapy and they are type IV cell mediated allergic hypersensitives. Puberty, pregnancy, child birth can also precipitate type I reactions. These reactions usually result in skin erythema, with edema and tenderness of peripheral nerves. The peak time for type I reaction is during the first 2 months of therapy up to 12 months.

Type II reaction / ENL :

Occur in 10% of patients with Borderline leprosy and in 20% patients with Lepromatous leprosy. These are type III hypersensitivity reactions with a systemic inflammatory response to immune complex deposition. The most common presenting symptoms are crops of painful erythematous nodules of the skin and subcutaneous tissue. Bullae, ulcers, necrosis can occur. The reaction usually manifests after few years of therapy. Although a single acute episode is possible, relapses occur immediately or over several years. Associated fever, malaise, iridocylitis, dactylitis, orchitis and proteinuria may be present.

Lucio phenomenon is an unusual type II reaction. It is common in Mexico and Central America and is characterized by cutaneous heamorrhagic infarcts in patients with diffuse lepromatous leprosy.

Ocular complications during lepra reaction :

The type I and type II reactions encountered during the course of the disease cause ocular involvement within days. Type I lepra reactions usually cause involvement of ophthalmic division of the trigeminal nerve and zygomatic and temporal branches of the facial nerves. Lagophthalmos often develops as a result of type I reaction, especially when associated with an erythematous facial skin lesion. Type II reaction usually cause acute iridocyclitis .Type II reactions may develop in multibacillary patients with long standing untreated disease, but up to 50% patients develop ENL within first year of anti-leprosy treatment. Borderline lepromatous and lepromatous leprosy are in particular risk of acute iridocyclitis and episcleritis during treatment and needs yearly follow up.

Diagnosis

A diagnosis of leprosy can be arrived in majority by a proper clinical examination alone, which involves a detailed history as well. This procedure is called case taking which comprises of

1) Interrogation :

- Bio data of patients
- History of contact with other leprosy patients
- Previous treatment history
- Presenting compliant

2)Clinical Examination :

- A thorough inspection of the body for evidence of leprosy
- Palpation for thickened nerves

3) Laboratory diagnosis :

Tissue smear testing / slit skin smears:

An incision is made in the skin and scalpel blade is used to obtain fluid from the lesion. The fluid is then placed on the glass slide and stained by using Zheil-Neelson acid fast method or Fite method to look for the organisms. The bacterial index is then determined as the number of organisms per 100 bacilli. Skin smears have high specificity but low sensitivity because 70% of all patients with leprosy have negative smears. It detects most infectious patients.

4. Skin biopsy :

Skin biopsy samples are stained with hematoxylin-eosin and Fite-Faraco. It is the primary basis for laboratory diagnosis and categorization. The presence of an inflamed nerve in a skin biopsy is considered as standard criteria for diagnosis. A full thickness skin biopsy sample should be taken from an advancing border of an active lesion and should include epidermis and dermis. Skin smears that demonstrate acid fast bacilli strongly suggest the diagnosis, but the bacilli may not be demonstrable in tuberculoid (paucibacillary) form of the disease. The skin biopsy sample should be examined for morphological features and presence of acid-fast bacilli. Biopsy is useful for determining the morphological index (MPI) which is used in evaluation and treatment of patients. The MI is the number of viable bacilli per 100 bacilli in leprous tissue.

5) Nerve Biopsy :

A nerve biopsy can be useful in ruling out diseases such as hereditary neuropathies or polyarteritis nodosa. They also help to identify abnormalities in sub-clinical leprosy. It is the only way to diagnose definitively in patients with completely neuropathic forms of leprosy.

6) Foot pad culture :

Mouse foot pad inoculation is most sensitive in detecting Mycobaterium leprae than slit skin smears.

It is used for

1. Detection of drug resistance
2. Evaluation of potency of antileprotic drugs
3. Detection of viability of bacilli during treatment

The disadvantage of this method is that it is time consuming and requires 6-9 months before the results are obtained.

7) Histamine testing :

This test is used to diagnose post-ganglionic nerve injury. Histamine diphosphate is dropped on normal skin and affected skin. A pinprick is made through each site. The site forms a wheal on normal skin but not where nerve damage is present.

8) Methacholine sweat testing :

A intra-dermal injection of methacoline demonstrates the absence of sweating in leprous lesions. This testing is useful in dark skinned patients in whom the flare with histamine test cannot be seen.

Immunologic tests :

1. Lepromin testing :

This test indicates host resistance to M.leprae by assessing the patients ability to mount an granulomatous response against a skin injection of killed M. leprae. It results do not confirm the diagnosis, but they are useful in determining the type of leprosy. A positive testing

(>5mm) indicates cell-mediated immunity, which is observed in tuberculoid leprosy. A negative finding suggests a lack of resistance to disease and is observed in lepromatous leprosy. A negative test result also indicates a poor prognosis.

Procedure:

To perform this test, bacillary suspension is injected into forearm. An assessment of the reaction at 48 hours is called **Fernandez** reaction and indicates delayed hypersensitivity to antigens of M.leprae or Mycobacterium that cross react with M.leprae. When the reaction is read at 3-4 weeks it is called **Mitsuda** reaction and indicates that immune system is capable of mounting an efficient cell-mediated response.

2.PGL -1 :

This is a specific serological test. It is based on antibodies to phenolic glycolipid-1 – (PGL-1). This test has a sensitivity of 95 % for the detection of lepromatous disease, but only 30% for tuberculoid disease.

3. Lymphocyte Migration Inhibition test (LMIT) :

As determined by a lymphocyte transformation and LMIT, cell-mediated immunity is absent in lepromatous form of the disease but present in tuberculoid form of the disease.

Serology and polymerase chain reaction :

Although these tests are useful in detecting multibacillary disease, they are not widely used because they fail to detect early or milder forms of the disease reliably.

Serology can be used to detect antibodies to M.leprae specific PGL-1. This test is useful primarily in patients with untreated LL, as 90% of patients have antibodies. However antibodies are present only in 40-50% patients with paucibacillary disease.

PCR analysis can be used to detect and identify M.leprae. The technique is used most often when acid fast bacilli are detected but clinical/ histopathological features are atypical. It is not useful when AFB is not detected by light microscopy. M.leprae DNA can be detected by using RT-PCR in ocular tissues,when acid fast bacilli are seen in histopathological section and when the diagnosis of leprosy is inconclusive. RT-PCR for M.leprae DNA could be used as a rapid confirmatory test to identify the presence of M.leprae and therefore the diagnosis of leprosy. The development of one –step reverse transcriptase PCR (RT-PCR) may be most sensitive in detecting bacilli in slit smears and skin biopsy specimens. This RNA based assay is also effective in monitoring bacteria clearance during therapy.

Imaging studies :

Radiographs :

Plain radiographs are useful to detect and monitor leprosy induced bone changes. Resorption, fragmentation and mal-aligned fractures are common signs of leprosy induced bone changes. Medullary sclerosis or wavy diaphyseal borders indicate diaphyseal whittling.

Histologic findings :

In TT form well developed epitheloid granulomas are observed in the papillary dermis, often around neovascular structures. The granulomas are surrounded by lymphocytes which extend into epidermis. Langerhans giant cells are common. Dermal nerves are destroyed / swollen because of the granulomas. Acid fast bacilli are not observed. S-100 is useful in identifying nerve fragmentation and differentiating it .

In the LL form, a diffuse infiltrate of foamy macrophages is present in the dermis below the sub-epidermal grenz zone. An enormous number of AFB develop within foamy macrophages, singly or in clumps called globi. Lymphocytes are scant and giant cells are typically absent. Numerous bacilli invade the nerves but these are fairly well preserved with little infiltrate. Nodular / dermatofibroma-like lesions in LL, referred to as **histoid** leprosy result in fascicular arrangement of spindle cells in the dermis admixed with foamy macrophages that contain numerous bacilli.

Histopathology of ocular tissues discloses far more silent chronic iridocyclitis in leprosy patients than are diagnosed clinically. AFB can persist in the iris tissue even after completion of MDT. Smooth muscle disruption and destruction causes miotic pupil in leprosy and has been conclusively demonstrated histopathologically.

MANAGEMENT

The management of leprosy includes pharmacothreapy and physical, social, psychological rehabilitation. The goals of pharmacotherapy are to stop the infection, reduce morbidity, prevent complications and eradicate the disease. Since 1981 MDT has been advocated by World Health Organisation (WHO) and US.

MDT prevents dapsone resistance, reduces relapses, reactions and disabilities. The length of treatment ranges from 6 months to 2years. Patients are considered non-infectious within 1-2 weeks of treatment (usually after first dose)

Current WHO recommendations for treatment of leprosy are as follows :

Paucibacillary disease :

Dapsone 100mg/day plus rifampicin 600mg once a month for 6 months .

Multibacillary disease :

Dapsone 100mg/day plus rifampicin 600mg once a month plus clofazimine 300mg once a month and 50 mg /day for 1year.

MDT Regimens :

Treatment for lepra Reaction :

Reaction	Prednisolone	Clofazamine	Thaliodomide
Reversal reaction (Type1)	Up to 1mg/kg/day then gradually reduced		
ENL (Type 2)	Up to 1mg/kg/day then gradually reduced	Upto 300mg	Upto 400mg
Combination therapy is recommended in ENL Thalidomide should be avoided in women of child bearing age			

- Corticosteroid treatment is aimed at controlling acute inflammation, relieving pain and reverses nerve and eye damage. With treatment, approximately 60-70% of patients nerve function is recovered. If neuritis is absent, non-steroidal anti-inflammatory drugs may be useful.

Erythema nodosum leprosum :

The use of clofazamine in MDT substantially reduces the incidence of ENL to 5% clofazamine has also been used to treat ENL.

Thalidomide is effective in ENL except in case of neuritis / Iritis in which case, corticosteroids should be used. Other treatment therapies reported to be effective include colchicine, pentoxiphylline, cyclosporine A, intravenous immunoglobulin (IVIG) and infliximab. Lowering the dose of dapsone may decrease the severity of bullae and ulcers

In lucio phenomenon, thalidomide is ineffective. Azathioprine / Cyclophosphamide with corticosteroids with or without plasmapheresis has been used.

Prevention and treatment of Deformites :

Potential deformities can be prevented by educating patients about how to minimize existing nerve damage and by treating any sequlae of this damage. Close follow up is important to ensure patient compliance.

Emergency surgery may be necessary if a patient with profound inflammation presents with nerve abscess / loss of nerve function secondary to compression.Prompt recognition and surgical drainage of the abscess can often restore nerve function.

Reconstructive surgery can be used to repair nasal collapse in LL.Other surgery may be needed to improve function or for cosmesis, Contractures can be surgically repaired .

Management of ocular complications of leprosy :

Madarosis	Island of neurovascular pedicle graft from the scalp
Upper lid ectropion	Blepharoplasty with correction of lid inversion
Lower lid ectropion	Tarsal strip procedure
Trichiasis	Cryoablation of abnormal lashes
Dacryocystitis Dacryoadenitis	Systemic antibiotics with dacryorhinostomy / dacryocystectomy. Systemic antibiotics with anti-inflammatory drugs
Lagophthalmos with exposure	Acute : Immediate treatment with prednisolone, thalidomide or clofazamine. Chronic : Eyelid exercise using maximum effort with artificial lubricants . Tarsorraphy / temporalis muscle transfer.
Limbal lepromas	Systemic antileprotic therapy
Episcleritis and scleritis	Topical / systemic anti-inflammatory agents
Corneal hypesthesia	Patient education about regular surveillance Eye protection with sun glasses & lubricants
Acute iridocyclitis Chronic iridocyclitis	Treatment of systemic ENL if present Topical steroids & mydriatics / cycloplegic agents , IOP monitoring Topical mydriatics Topical steroids if anterior chamber reaction is severe
Cataract	Cataract extraction with or without implantation of IOL depending on the presence or absence of uveitis
Glaucoma	Standard management of open angle glaucoma ,angle closure or complicated glaucoma with synechiae

Drug and side effects :

Rifampicin (RFP) :

The drug is administered in a single monthly dose, a protocol for which no significant toxic effect has been reported. Exceptionally bactericidal against M.leprae and single dose of 600mg of RFP is capable of killing 99.9% or more of viable organisms. However the rate of killing is not proportionately enhanced by subsequent doses. It has been suggested that RFP may exert a delayed antibiotic effect for several days during which organisms multiplication is inhibited. The high bactericidal activity of RFP made feasible the application of the single monthly dose, which is cost-effective for leprosy control programs.

Side effects :

Red colouration of urine and other side effects include skin rash , peripheral neuropathy, hemolytic anemia, flu-like syndrome.

Di-amino diphenyl sulfonoe (DDS, dapsone) :

Until widespread resistant strains to drug were reported, dapsone which is bacteriostatic / weakly bactericidal against M.leprae was for years the mainstay treatment regimen for leprosy. Subsequently its use in combination with other drugs has become essential to slow or prevent the development of resistance. The drug has demonstrated an acceptable level of safety in the dosage used in MDT.

Side effects :

Besides occasional cutaneous eruptions, side effects that necessitate discontinuation are rare. Patients known to be allergic to any of sulfa drugs should be spared dapsone. Anemia, hemolytic and methemoglobinemia may develop but are more significant in patients deficient for glucose-6-phosphodihydrogenase (G6PD)

Clofazimine (CLF) :

CLF which preferentially binds to mycobacterial DNA inhibits both mycobacterial growth and exerts a slow bactericidal effect on M.leprae. Because of its anti-inflammatory properties it is suggested for the erythema nodosum leprosum reactions by mechanisms still poorly understood.

Most active when administered daily , dosage used for MDT is well tolerated and has not shown significant toxicity. Because CLF is a repository drug, stored in the body after administration and slowly excreted. It is given as a loading dose of 300mg once a month to ensure that the optimal amount of CLF is maintained in the body tissue even if patients occasionally miss the daily dose.

Side effects :

Brownish black discolouration and dryness of skin. These usually disappear within few months of treatment suspension. Other side effects include abdominal pain, diarrhea, phototoxicity.

Ofloxacin (oflx):

OFLX a synthetic fluoroquinolone acts as a specific inhibitor of bacterial DNA gyrase and has shown efficiency in the treatment of M.leprae. Chromosomal resistance of negligible clinical relevance has been reported .

Minocycline (MINO) :

MINO is a semisynthetic tetracycline in susceptible organisms and induces bateriostasis by inhibiting protein synthesis.

However from the curative and cost-effectiveness points of view ,the WHO recommended MDT remains to date the best combination regimen of the worldwide leprosy control programme.

Laboratory monitoring for drugs used to treat leprosy includes :

Drug	Laboratory studies	Frequency
Initial studies for all drugs	CBC, platelets	Baseline
DDS	G6PD,CBC	Every 6 months
RFP	CBC,platelets,hemoglobulin	Every 3 months
CLF	No recommended lab studies	Every 3 months
Thalidomide	CBC	Every 2 months

Prevention

The basic factors in the prevention of leprosy in endemic regions are:

1. Case finding and prompt treatment of all cases found, with multidrug therapy.
2. Keeping close contacts of patients under surveillance.
3. Vaccination of all young children, especially those born in leprous families and to lepromin negative contacts of index cases with BCG vaccine.
4. Improvement in socioeconomic condition.
5. Health education and publicity about leprosy and about early presentation for diagnosis and cure by multidrug therapy

Attempts to develop a vaccine against M.leprae are being made that may induce immunity in non-infectious patients and a high level of immunity in leprosy patients. This is based on the theory that cross immunity exists between TB and leprosy. Thus BCG is a cheap and safe substitute until a specific anti-leprosy vaccine is discovered. But the extent to which elimination and eradication of leprosy will depend mainly on improvement in socioeconomic conditions as Latapi the renowned Mexican Leprologist said` Leprosy cannot be completely rooted out with physicians, control officers, leprosaria and propaganda'. It will disappear when the economic and cultural factors change, because leprosy is the thermometer of civilization.

The strategy for leprosy elimination :

The following actions are part of the ongoing leprosy elimination campaign :

1) Ensuring accessible and uninterrupted MDT services are available to all patients through flexible and patient friendly drug delivery systems.
2) Ensuring the sustainability of MDT services by integrating leprosy services into general health services. Building the ability of general health workers to treat leprosy.
3) Encouraging self reporting and early treatment by promoting community awareness and changing the image of leprosy.
4) Monitoring the performance of MDT services the quality of patients care and the progress being made towards elimination through national disease surveillance systems.

AIMS AND OBJECTIVES

1. To analyse the ocular manifestations of leprosy in a hospital population.
2. To analyse the incidence of ocular complications and visual outcome.

MATERIALS AND METHODS

A prospective and descriptive study on ocular manifestations of leprosy and its management was conducted in Government Rajaji Hospital – Department of ophthalmology, Madurai. This study was conducted from January 2007 to Dec-2007, during which 46 patients with ocular manifestations were analyzed. In this study all the patients with systemic leprosy who presented to the department of Dermatology outpatient were referred to the department of Ophthalmology and screened for ocular manifestations.

Inclusion criteria :

All leprosy patients who attended department of ophthalmology, GRH in the period from Jan-2007 to Dec -2007.

Exclusion criteria :

Patients with co-morbid condition like HIV were excluded from the study.

Clinical evaluation :

In all these patients demographic data like age, sex, place of residence were documented. A detailed history regarding systemic symptoms of leprosy like defective vision, redness, pain, loss of eyelids were documented.

An elaborate treatment history regarding

(i) Year of onset of skin lesions and the latency period if any, of the start of systemic treatment.

(ii) Duration and regularity of treatment.

(iii) Type of treatment – monodrug / multidrug were elicited.

The patients were examined for ocular manifestations and systemic manifestations of leprosy.

Ocular examination included :

(i) Best corrected visual acuity.

(ii) Slit lamp examination for the type of keratic precipitates, anterior chamber reactions, iris features, posterior synechiae, lens changes and scleritis.

(iii) Dilated fundus examination by indirect ophthalmoscopy, +90D slitlamp biomicroscopy.

(iv) **SLE :** To look for episcleritis, scleritis, keratitis, exposure keratopathy, uveitis and cataract.

(v) **Corneal sensation :** Tested by asking the patient to look up and applying tail end of wisp of cotton on the cornea 2mm from the limbus at the 6’ clock position and categorizing the sensation as normal if the patient responded by retracting the head (or) closing the eyelids. It is impaired if the patient didn’t.

(vi) Detailed external ocular examination done with the help of torch light to look for madarosis, lagophthalmos, lid nodules.

Systemic evaluation was done to assess

1) Skin lesion
2) Neuropathies
3) Deformites

Based on this patients were grouped according to WHO classification of visual impairment and blindness.

Grading	Category of visual Impairment	Best corrected visual acuity in the better eye
0	Normal	6/6 to 6/18 i.e – can see 6/18 or better
1	Visual Impairment	<6/18 to 6/60 i.e – cannot see 6/18 can see 6/60
2	Severe Visual Impairment	<6/60 to 3/60 i.e – cannot see 6/60 can see 3/60
3	Blind	<3/60 to 1/60 i.e – cannot see 3/60 can see 1/60
4	Blind	<1/60 to only light perception i.e –cannot see 1/60 can see light
5	Blind	No light perception i.e – cannot see light
6	Undetermined or unspecified	

Intra ocular pressure was recorded in all patients above 40 years by schiotz tonometer. Gonioscopy was done with Goldmann goniolens in suspected cases of narrow angles and graded according to shaffers classification. Fields were done in Humphery perimeter in selected cases.

After establishing the diagnosis, appropriate treatment was started. Patients with acute granulomatous or non- granulomatous uveitis were treated with topical steroids – 1% prednisolone acetate frequency being determined by severity of iritis at the time of presentation, cycloplegics –

homatropine eyedrops 2 times/day and oral non-steroidal anti-inflammatory agents – tablet Ibubrofen 500 mg twice a day. Patients with episcleritis and scleritis were treated with topical steroids like % prednisolone acetate. Patients with severe or recurrent intra- ocular inflammation suspected to be due to active leprosy were started on anti-leprosy treatment and systemic steroids after consulting the dermatologists. Anti- glaucoma medications were started in patients with raised intra-ocular pressure. Secondary angle closure glaucoma patients with cataract underwent cataract extraction with intraocular lens implantation after ocular inflammation is controlled with topical steroids or systemic steroids. Lateral tarsorraphy was done in patients with lagophthalmos with exposure keratopathy. Patients were followed over subsequent visits. During each visit BCVA, ocular status and skin lesion were assessed.

At the end of the study period, all the data were analyzed. The pattern of ocular involvement in these patients were analyzed. The correlation between anti-leprosy treatment and ocular involvement were analyzed. The visual outcome of the treatment were analyzed for those patients who had atleast three follow up's during the study period.

PROFORMA

Name : Age : Date :

Sex : 1: Male, 2 : Female Occupation :

Address :

History (Present – 1, Absent – 2)

Skin Lesion Weakness or anaesthesia of limbs
Nasal symptoms Edema of legs
Year of onset of skin lesion ____ year of diagnosis___year of treatment

Type of Leprosy

1 – TT 2 – BT 3 – BB 4 - BL 5 - LL

Ocular symptoms of Leprosy

1. Pain 2. Redness 3. DV 4. Loss of eyebrows 5. Inability to close lids

Occurrence of ocular symptoms

1. During treatment 2. After treatment

Lepra Reaction

1 – Present , 2 – Absent

Type – 1	Erythema of existing lesions	Nerve palsy	
	Edema of existing lesion		
Type – II	Fever	Epistaxis	Edema of legs
	Epididymoorchitis	Malaise	Joint pain
	New skin lesions	Dactylitis	Others

Precipitating factor

1. Pregnancy 2. Vaccination 3. Trauma 4. Recent ALT 5. Nil

Ocular symptoms of Lepra reaction

A) 1. Pain 2. Redness 3. Photophobia 4. DV 5. Floaters

B) No.of episodes of Lepra reaction

C) Time of occurrence

1. Before treatment 2. During 3. After treatment

Treatment given for ocular symptoms of lepra reaction

1. Topical steroids 2. Systemic steroids 3. ALT 4. Antiglacoma drug

5. NSAID 6. Thalidomide 7. Others

Dosage : _____

Duration : _____

Treatment History for leprosy

1. Multidrug 2. Monodrug 3. Mono to multi drug 4. Details not known

5. Treatment not taken

A) Drugs : Dapsone Rifampicin Clofazamine Steroids Others

Dosage : _____

Duration : _____

B) Total duration of treatment

C) Treatment Status : 1. Completed treatment 2. Undergoing treatment

D) Compliance : 1. Regular 2. Irregular

EXAMINATION : Systemic :

Skin : Hypopigmented patches 1. 0 2. < 6 3. ≥ 6

Neuropathy : 1. Trigeminal 2. Facial 3. Ulnar 4. Radial 5. Median 6. Greater auricular 7. Deep peroneal 8. Posterior tibial 9. No neuropathy

1. Right 2. Left 3. Both

Deformities of Extremities Nasal deformities Present – 1, Absent - 2

Ocular Examination :

Laterality : 1. Unilateral 2. Bilateral 3. One eyed

Manifestations	R E	L E	Manifestations	R E	L E
Madarosis			Iris atrophy		
Lagophthalmos			Iris nodules		
Lid nodules			Cataract		
Episcleritis			Lepra pearls		
Scleritis			Others 1. Corneal ulcer 2. Adherent leucoma 3. Phthisis bulbi 4. Dacryocystitis		
Corneal sensation			BCVA		
Iridocyclitis			IOP		
Granulomatous			Fundus 1. Normal 2. Glaucomatous 3. Others 4. Hazy view		
Non granulomatous					
Acute / chronic					

Surgery :

1. Unilateral 2. Bilateral 3. Not done 4. combined surgery

Type of surgery : _____ 1. R E 2. L E

Post op. Complications :

1. Present 2. Absent

Post of vision : _____

	Follow up	I	II	III	IV	V
A	BCVA (RE) BCVA (LE)					
B	Skin lesions					
C	Ocular lesions (RE) (LE)					
Improved - 1 Static - 2 Worsened - 3						

Treatment :

Investigations :

RESULTS

In this study, 46 patients with ocular leprosy were analysed. Among 46 patients, 4 had lepra reaction. Patients demographic characteristics are shown in table 1 and 2. Most of the patients were in 6^{th} – 7^{th} decade of life. Majority of patients (80.43%) were males.

Type of leprosy is shown in table 3. Majority of patients (80.43%) had lepromatous leprosy. Among lepromatous leprosy, lepra reactions were noted in 4 patients. The time of occurrence of ocular manifestations in leprosy is shown in table 4. Ocular manifestations were predominantly seen (91.3%) after treatment.

The details of anti-leprosy treatment are shown in table 5and 6. Among 46 patients 44 of them had already taken treatment (94.4%). In the remaining 2 patients type of treatment was not known in 1 patient and 1 patient didn't receive treatment. The predominant regimen were multidrug therapy (54.34%) and monotherapy (33.3%).

67.39% of patients had successfully completed their treatment with good compliance. Systemic features such as skin lesions, neuropathy are shown in the table 8 and 9 respectively. Among them only 17.39% had skin lesions, the remaining 82.61% had no **skin lesions**. Peripheral neuropathy was observed in 31.8% of patients. Ulnar nerve was the most common neuropathy followed by common peroneal nerve and greater

auricular nerve in both the subgroup of patients. Data obtained from (**ocular evaluation**) are discussed below. Table 10 shows that majority (72.72%) of patients had bilateral involvement. 12 patients had unilateral involvement and 6 were monocular. Table 11 shows that madarosis (80.30%) was the most common adenexal ocular manifestation in both the sub groups.

Table 12 and 13 shows the pattern of **ocular involvement** in these patients. Chronic granulomatous uveitis was seen in 36.52% of eyes. Decreased corneal sensation was observed in 37.1 % of patients . Corneal leucoma was observed in (6.12%) and corneal ulcer was observed in (2.04%) of patients . Episcleritis (4.54%) and scleritis (4.54%) were reported. 45 eyes out of 66 eyes showed iris atrophy and iris nodules were observed in 1 patient. Lepra pearls were seen in 1 patient.

Table 14 shows the analysis of **type of cataract.** 30 eyes had cataract of which 17 were **complicated cataract**, 13 were senile type. Findings of posterior segment are showed majority of patients (84.84%) had normal fundus. Glaucomatous disc was observed in 3.03% patients. Fundus view was hazy and could not be assessed due to cataract in 10.68% patients.

Intraocular pressure was recorded in all patients. Majority had normal IOP. Ocular hypotony was seen in 6.06% of patients. Glaucoma was seen

in 3.03% of patients. Antiglaucoma medications were required in 11.11% of patients.

The details of **cataract surgeries** were shown in table. 20 out of 66 eyes underwent cataract surgery. One patient underwent combined procedure (cataract surgery with trabeculectomy). 95% had good visual outcome.

WHO grading of visual impairment of the patients were shown in table. 10.86% had severe visual impairment. 10.88% of patients met with blindness criteria.

Potentially sight threatening lesions (PSTL) are those that cause visual impairment and blindness. PSTL include lagopthalmos, corneal hyposensitivity, keratitis, iris involvement and post operative inflammation.

Lagophthalmos (4 patients) were examined for adequate Bells phenomenon and corneal sensation. Patients with lagophthalmos with indadequate Bells phenomenon were treated with temporary lateral tarsorraphy (8 patients). They were observed for exposure keratitis, secondary bacterial keratitis during their follow up.

Patients having neurotrophic and neuroparalytic keratitis (7patients) were observed for exposure keratitis and secondary bacterial keratitis. Two patients were not compliant with their follow up and developed severe

secondary bacterial keratitis and perforation. Our best treatment prevented them developing blindness and gained vision 4/60.

Cataract surgery in inflamed eyes is a challenge to even an experienced ophthalmic surgeon. Preoperatively all patients were evaluated in Slit lamp to rule out active inflammation. All patients were preoperatively treated with hourly steroid eye drops.

Due to our meticulous surgery and minimum tissue handling during surgery we landed up with few post operative complications. Patients were given intense steroid therapy depending upon the severity of inflammation. Inspite of our best efforts, 2 patients developed severe post op inflammation leading to deterioration of vision upto 6/60.

Remaining 52.17 % patients had normal visual acuity. Majority of patients (66.67%) of patients were treated with steroids. Anti-leprosy treatment was restarted in 19.44% of patients. One patient with history of lepra reaction were treated with thalidomide.

The **follow up and treatment response** of these patients are analysed. 19 patients had come for more than 3 follow ups. Ocular inflammation had improved in 75% patients, static in 8.33%. In these patients with history of lepra reaction only one patient had come for regular follow up and there was good improvement in ocular condition. The skin lesion was static in all patients.

Table -1 Age distribution

Age group	No.of leprosy patients
30 - 39	2
40 - 49	7
50 - 59	18
60 - 69	16
70 - 79	3
Total	**46**

Most common age group 6^{th} – 7^{th} decade

Table - 2 Gender

Gender	No .of leprosy patients	Percentage
Male	37	80.5
Female	9	19.5
Total	**46**	**100**

Table – 3 Type of leprosy

Type of leprosy	No. of leprosy patients	Percentage
Tuberculoid	9	19.5
Lepromatous	37	80.5
Total	46	100

Table -4 time of occurrence of ocular symptoms of leprosy

Time of occurrence of ocular symptoms	No.of leprosy patients	Percentage
During treatment	4	8.7
After treatment	42	91.3
Total	46	100

Table – 5 Time of occurrence of lepra reaction

Treatment status	No .of patients with lepra reaction
Before start of treatment	0
While on treatment	3
After completing treatment	1
Total	4

Table - 6 Treatment History

Type of medical treatment	No .of leprosy patients
Multidrug	25
Monodrug	13
Monodrug to Multidrug	6
Details not known	1
Treatment not taken	1
Total	46

Table - 7 Compliance

Compliance	No.of leprosy patients
Regular	30
Irregular	14
Treatment details not known	2
Total	46

Table - 8 Skin lesions

Hypopigmented patches	No.of leprosy patients
Nil	38
<6	7
>=6	1
Total	46

Table -9 Neuropathy

Neuropathy	No . of leprosy patients
Trigeminal	1
Facial	4
Ulnar	17
Radial	0
Median	0
Greater auricular	5
Common peroneal	8
Posterior tibial	1
Nil	26

Table -10 - Laterality

Laterality	No .of eyes
Unilateral	12
Bilateral	48
One eyed	6
Total	66

Table - 11 Ocular Adenexal manifestations

Clinical signs	No . of eyes
Madarosis	53
Lagophthalmos	14
Lid nodules	0
Chronic dacryocystitis	3

Table -12 Ocular manifestations

Clinical signs	No .of eyes
Episcleritis	3
Scleritis	3
Decreased corneal sensation	24
Acute granulomatous uveitis	16
Chronic granulomatous uveitis	24
Acute nongranulomatous uveitis	6
Chronic nongranulomatous uveitis	4
Adherent leucoma	4
Corneal ulcer	2

Table -13 Cataract

Type of cataract	No. of eyes	Percentage
Complicated cataract	17	25.5
Senile cataract	13	20
Nil	36	54.5
Total	66	100

Table -14 Grading of visual impairment

Grade	No .of eyes	Percentage
Normal	24	52
Visual impairment	12	26
Severe visual impairment	5	11
Blind	5	11
Total	46	100

Table -15 Immediate postoperative vision after cataract surgery

Best corrected visual acuity	No .of eyes
6/6 - 6/12	17
6/18 - 6/36	2
$\leq$ 6/60	1
Total	20

Table -16 Follow up

Number of follow up	No .of leprosy patients
Nil	15
1 - 2	12
3 - 5	19
Total	46

Table -17 Treatment response for inflammation

Treatment response of inflammation	**No of leprosy patient**	
	Ocular	**Systemic**
Improved	16	0
Static	4	16
Worsened	2	0
Total	22	16

DISCUSSION

Leprosy is a disease which is still endemic in 120 developing countries and also contributes to significant cause of blindness. Most of the blindness is avoidable and could have been prevented by early diagnosis of ocular leprosy, early systemic anti-leprosy treatment, timely treatment of immune reactions and prompt treatment of ocular complications. Our study results were consistent with this finding.

According to longitudinal study on ocular leprosy (Ethiopia, India & Philippines) 2.8% are blind at the time of diagnosis and 11% had potentially blinding complications. Our study results were consistent with this findings.

The demographic profile of these 46 patients in this current study is consistent with published reports. The age group of presentation in our study was between 4^{th} -8^{th} decade majority being in their 6^{th} -7^{th} decade. This is similar to previous reports. The sex incidence in our study revealed a male:female ratio (4:1) which is comparable to other studies in literature. The male preponderance is because males in general expose themselves to greater risks of infection as a result of their life style. This male preponderance is seen even in patients with a history of lepra

reaction, on the other hand women may not tend to seek medical help even when it is required.

It is well known that persistence or recurrence of inflammation can occur long after systemic infection was treated with ALT. Though routine skin smear may be negative after completion of treatment, the persistence of M.leprae in the fibrosed nerves may be responsible for chronic uveitis seen in these patients. Espirito et al had reported an incidence ranging from 5.3% to 63% of chronic iridocyclitis in patients treated for leprosy.

Systemic evaluation revealed that majority had no skin lesions at the time of presentation of ocular symptoms. The most common neuropathy was **ulnar nerve** followed by **deep peroneal nerve** in both the subgroup of patients. Deformities of the extremities and depressed nasal bridge were found to be more common in lepromatous type.

In ocular evaluation **madarosis** was the most common ocular adenexal manifestation seen in our study. These findings are consistent with previous reports. **Lagophthalmos** was seen in 33.3% patients. In patients with Lagophthalmos the Bells phenomenon was assessed. Patient with adequate Bells phenomenon (4 patients) were treated with lubricants. Patients with inadequate Bells phenomenon were treated with **temporary lateral tarsorraphy** (8patients). The reports of other abnormalities of lid

like entropion and ectropion were very few. Among 46 patients 5 patients had phthsis bulbi at presentation, the reason for phthisis was not evaluated.

The commonest form of uveitis in lepromatous leprosy is chronic low grade insidious type of uveitis. In our study the commonest type of uveitis is chronic low grade uveitis which is also consistent with this fact.

Iris atophy is a common finding in the chronic uveitis. Iris pearls are chalky white particles in the superficial connective tissue of the pupillary margin Mithal et al had reported an incidence of these findings which are compared with our study. Iris atrophy was seen in 60 %.

Episcleritis and **scleritis** were seen in 4.54% of patients. None of the patients with history of lepra reaction had scleritis or episcleritis. Tajamul khan et al in his study found the incidence of episcleritis to be around 1%.

Leprotic pearl were seen 1 patient and iris nodules were seen in 1 patient. According to a study Ebenezor et al it was found that iris atrophy continues to develop in 3% of patients with MB leprosy every year after they complete their 2 year course of MDT and is associated with age, increasing loads of mycobacteria, subclinical inflammation, cataract and corneal opacity.

CONCLUSION

In this prospective and descriptive study done in Government Rajaji Hospital during January 2007 to December 2007, 46 patients with ocular leprosy were analysed.

Among these 46 patients who presented with ocular leprosy, 4 patients had history of lepra reaction.

Cataract surgery alone was done in 19 patients. Combined surgery was done in 1 patient. 95% of patients had good visual outcome after cataract surgery.

Temporary lateral tarsorraphy was done in 8 patients of lagophthalmos having inadequate Bells phenomenon.

Majority of these patients had developed ocular manifestations despite completing anti-leprosy treatment with good compliance, thus emphasizing the importance of monitoring patients even after completing treatment.

Majority of patients treated for ocular inflammation had good visual outcome.

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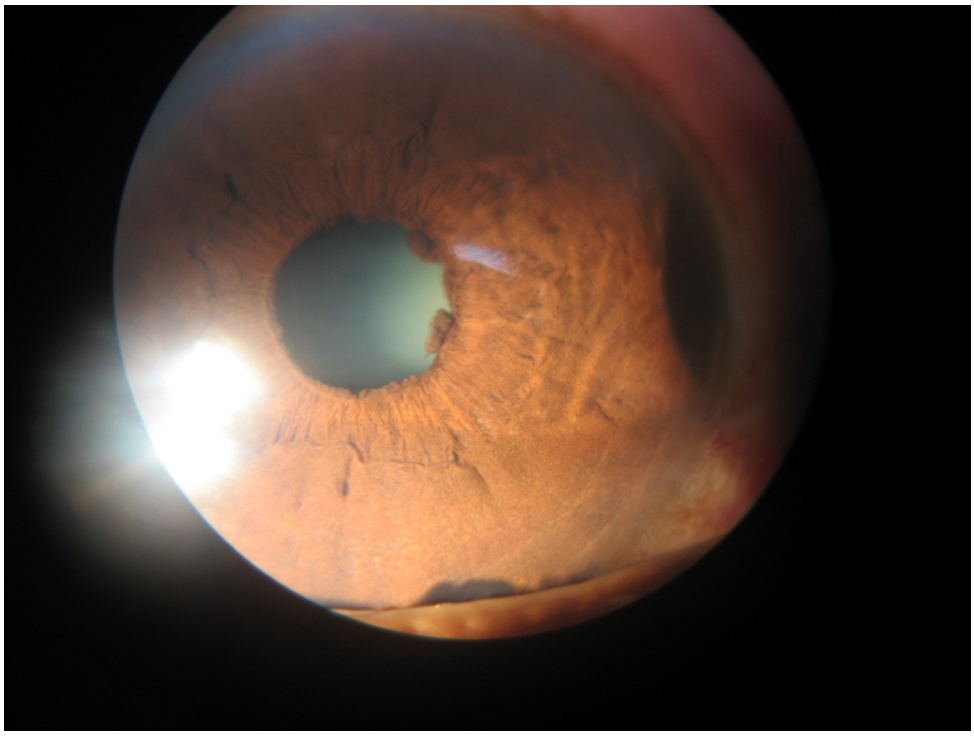
ABBREVIATIONS

AFB	ACID FAST BACILLAI
CBC	COMPLETE BLOOD COUNT
ENL	ERYTHEMA NODOSUM LEPROSUM
G6PD	GLUCOSE -6 PHOSPHATASE DEHYDROGENASE
HLA	HUMAN LEUCOCYTE ANTIGEN
IG	IMMUNOGLOBULIN
KP	KERATIC PRECIPITATES
LL	LEPROMATOUS LEPROSY
MB	MULTI BACILLARY
MDT	MULTI DRUG THERAPY
M.LEPRAE	MYCROBACTERIUM LEPRAE
TT	TUBERCULOID LEPROSY
TNF	TUMOUR NECROSIS FACTOR
WHO	WORLD HEALTH ORGANISATION
NLEP	NATIONAL LEPROSY ERADICATION PROGRAMME
NLCP	NATIONAL LEPROSY CONTROL PROGRAMME

LATERAL TARSORRAPHY - RE

PAUCI BACILLARY BLISTER PACK



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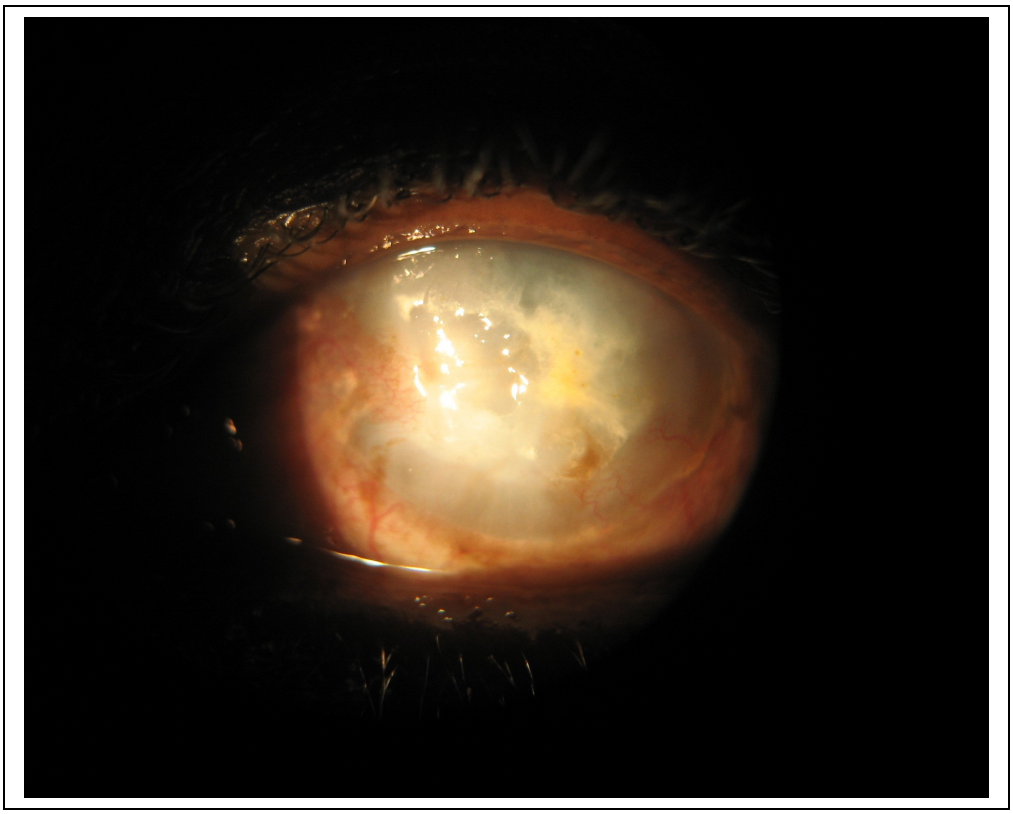

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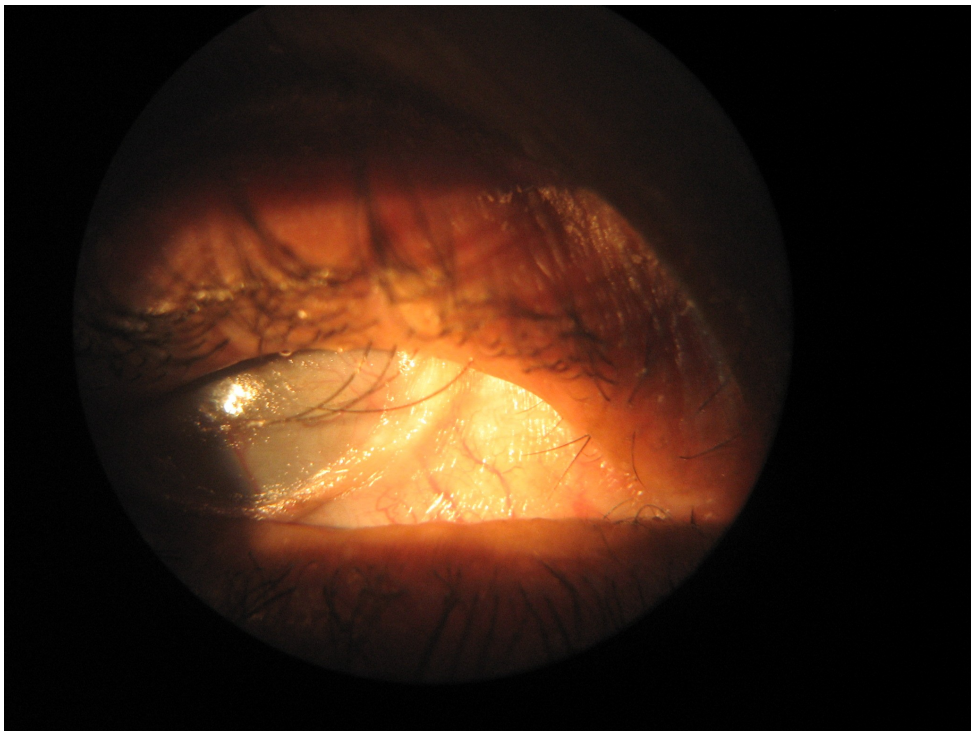
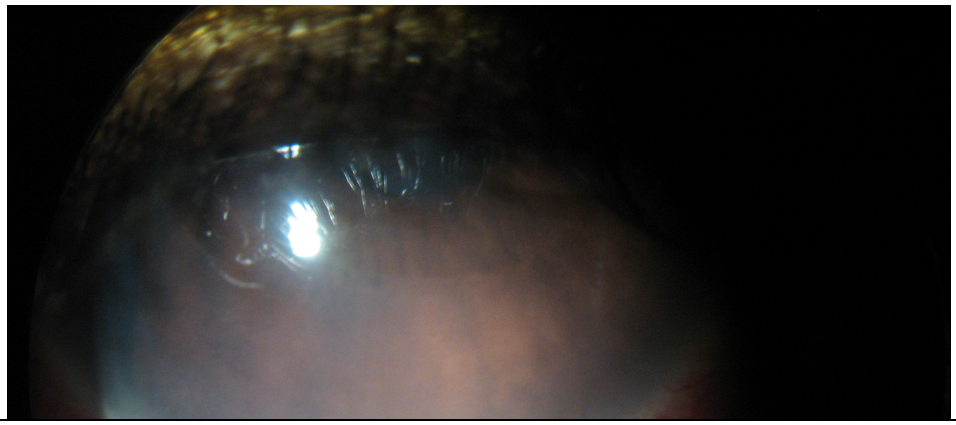
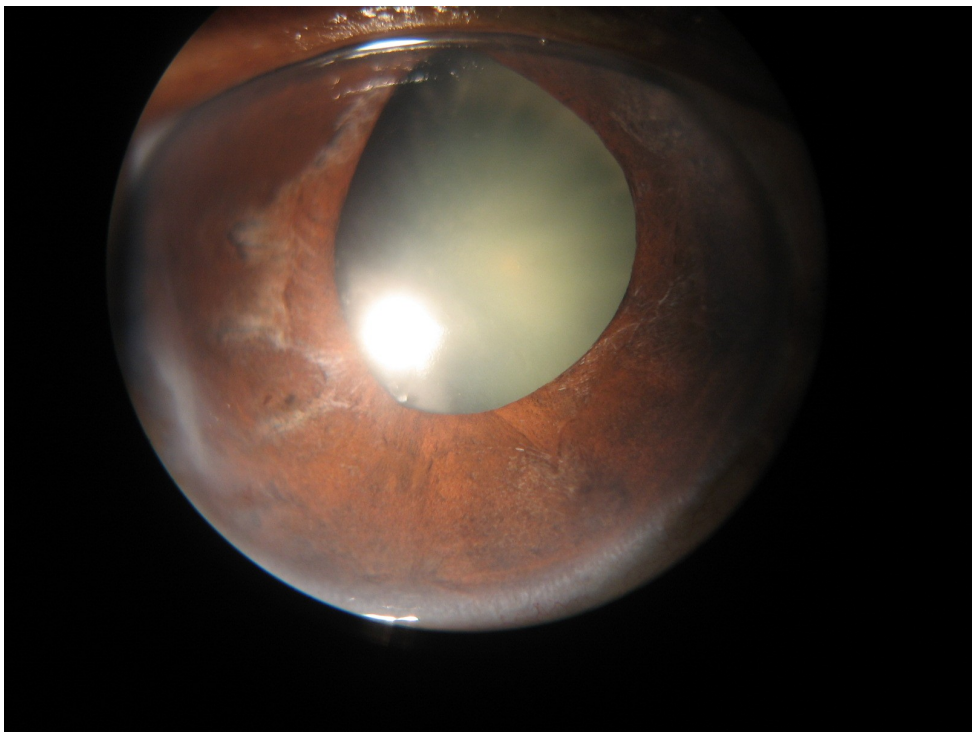


EPISCLERITIS

IRIDOCYCLITIS WITH HYPOPYON



IRIS – ATROPHIC PATCHES



CORNEAL ULCER WITH HYPOPYON